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History, institutional care and recent physiological therapeutic advances as adjunct measures in the management of the functional mental patient

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HISTORY, INSTITUTIONAL CARE AND RECENT PHYSIOLOGICAL
THERAPEUTIC ADVANCES AS ADJUNCT MEASURES IN THE
MANAGEMENT OF THE FUNCTIONAL MENTAL PATIENT

By

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PREFACE

It is truthfully said that, until recent years, the care and treatment of the insane has been sadly neglected. Insanity was considered as a divine punishment even as late as the nineteenth century, and it has only been within recent years that the true significance of mental disease as a medical problem has been realized.

During the last decade we have witnessed an epoch in psychiatric therapeutics. Numerous methods have been advanced as adjuncts to the treatment of the functional mental patient. The efficacy of these methods has given new impetus to research, and although these methods are rapidly becoming legion, it is not to be inferred that they are at present exhaustive.

In the first section of this paper a resume of the history of the early care of the insane, of both organic and functional origin, is included. This is followed by a discussion of the institutional care of the mentally ill, including a discussion of recently advocated institutional methods.

The remaining sections are devoted to a review of the literature relative to recent methods of the application of drugs as therapeutic adjuncts in the treatment

of functional mental patients. As this paper is limited to a consideration of drug therapy, mention of the recently advocated prefrontal lobotomy method of treatment is not included. Particular emphasis has been placed upon the technic of the application of these drugs. It is not the author's intention to infer that these more recent methods may supersede the methods of treatment already in use, including psychotherapy, occupational therapy, recreational therapy, and many others. However, these more recent methods may serve as a valuable adjunct when used as a supplement to the already existing forms of therapy.

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INTRODUCTION

It has been reliably estimated that of the seven thousand infants born each day in the United States about two hundred and seventy, or one in twenty six, eventually become incapacitated by abnormalities of the mind.(1) Likewise, it is known that approximately 75,000 new patients are annually admitted to state institutions for the insane with a total of 147,621 new patients admitted yearly to all institutions caring for the insane in the United States.(1,2) Of the total 808,445 available hospital beds in the United States, the mental group constitutes 445,867 or fifty five per cent of the whole.(2)

Strecker (1) lists the incidence of the psychoses as follows:

Dementia Praecox-----	27.2%
Manic Depressive-----	12.9%
Involuntional Melancholia-----	3.0%
Paranoia-----	.5%
Psychoneurosis-----	2.4%

Thus the psychoses and neuroses constitute forty six per cent of all mental disease. He further states that it is conservatively estimated that between sixty five and seventy five per cent of the psychoses which are comparable to what the internist would designate "acute" are recoverable.

Functional psychoses include all psychoses in which constant organic and toxic factors have not been ascertained.

This paper is confined to a consideration of the treatment of functional mental disease. An attempt is made to depict the history of therapy and institutional care of these patients. Emphasis has been placed upon the present status of hospital care and upon the technic of recent therapeutic methods.

The therapeutic methods considered have been restricted to medical (drug) therapy. These drugs are considered in the following sequence: history, selection of patients, technic of administration of therapeutic agents, reactions, complications of treatment, results, and clinical and laboratory findings. It is acknowledged that therapy is predominantly empirical, but wherever rationale has been proffered, it will be included.

No space has been devoted to a review of the etiology of these conditions, and psycho-therapeutic and surgical methods have been intentionally omitted.

HISTORY

"Foul whisperings are abroad: unnatural deeds
Do breed unnatural troubles: infected minds
To their deaf pillows will discharge their secrets.
More needs she the divine than the physician-"
Shakespeare

The distinction between those mentally and those physically ill is of extreme antiquity. In the earliest historical records we find that insanity was referred to as possession of the body by demons and evil spirits and, but more rarely, to the favor of the gods. This belief has persisted until comparatively recent times.

Dorcas and Shaffer (3) state that an Egyptian papyrus dating about three thousand B. C. has been discovered in which is set forth the proceedings of modern hypnotism. They state that the Medes, Chaldeans, and Indians were very familiar with the hypnotic state, and that the methods have probably been handed down through the priests of Egypt, The Persian Magi and the Levites. These authors suggest that the temple sleep induced by the priests was likely hypnotic.

Naturally the idea of demonological possession easily opened the way for flagrant abuses in the treatment of the insane. They were poorly sheltered, scantily fed, unclothed, chained, tortured, burned and beaten, all in an effort to drive out the demons.(1,4)

Strecker (1) states that the only interruption of this primitive point of view was the rational belief of the great Hippocrates (460-375 B. C.) and other Greeks of that period, who taught that "the brain is the organ of the mind."

Asclepiades of Bithynia (124 B. C.) was the first pioneer in the humane treatment of mental disorders, indeed as Friedreich observes "first taught us how to treat the insane." He noted that the frenzied patient has hallucinations whereas the maniacal patient has delusions. Reasoning that hallucinations are exaggerated in the dark, he discarded the antique practice of keeping mental sufferers in the dark by letting in broad daylight. For treatment he employed occupational therapy, exercises in promoting memory and fixing attention, music and wine to promote sleep.(5)

Tuke (6) states that among our Saxon ancestors (sixth century) the treatment of the insane was a curious compound of pharmacy, superstition and castigation. Demoniacal possession was fully believed and, as is well known, exorcism was practiced by the Church as a recognized ordinance. He states that it appears that the Saxon leeches derived much of their knowledge directly from the Romans and through them from the Greeks.

He cites from a collection of articles entitled "Leechdoms, Wortcunning and Starcraft of Early England" (Medicine, Herb Treatment and Astrology) numerous methods employed by these Saxon leeches.

The directions for a "fiend sick man" were as follows. "Take a spew-drink, namely lupin bishopwort, henbane, cropleek. Pound them together; addale for a liquid, let it stand for a night and add fifty libcorns (seeds of wild saffron) or cathartic grains and holy water."

"Another mixture compounded of many herbs and of clear ale was to be drunk out of a church bell (acolytes' bell) while seven masses were to be sung over the worts or herbs, and the lunatic was to sing psalms, the priest saying over him Domine, sancte pater omnipotens."

Mandrake administered in a draught of warm water was prescribed for witlessness; and periwinkle (Vinca pervinca) was regarded as of great advantage for demoniacal possession and "various wishes". Directions included were, "When thou shalt pluck this wort, thou shalt be clean from every uncleanness and thou shalt pluck it when the moon is nine nights old and eleven nights and thirteen nights and thirty nights and when it is one night old."

Wolf's flesh well dressed and sodden was to be eaten by a man troubled by hallucinations.

Other directions included, "In case a man be lunatic take a skin of mere swine (sea pig or porpoise) work it into a whip, and swinge the man therewith; soon he will be well. Amen."

Tuke states that bowsening (ducking) was also practiced. In support of this statement he cites the following description from "Leechdoms, Wortcunning and Starcraft of Early England." "A stronge fellowe, provided for the nonce tooke him and tossed him up and downe alongst and athwart the water untill the patient by forgoing his strength had somewhat forgot his fury." "The patient was then conveyed to the church and certain masses sung over him. If there appeared small amendment he was bowsened "again and againe while there remayned in him any hope of life for recovery."

Bartholomew the Englishman (Bartholomaeus Anglicus) writing in the middle of the thirteenth century was a proponent of the humane treatment of the insane. He states, "The medicine of them is, that they be bound, that they hurt not themselves and other men. And namely, such shall be refreshed, and comforted, and withdrawn from the cause and matter of dread and busy thoughts. And they must be gladdened with instruments of music, and some deal be occupied." (7)

We may conclude that the early history of the care of the insane was predominantly barbaric with little or

no scientific approach and with few advocates of humane treatment.

These conditions persisted throughout the Middle Ages. Strecker (1) states that this state of affairs existed even during the nineteenth century. Haggard (4) relates that the medieval Christians built hospitals and everyone who was physically ill was admitted. The insane were excluded. He states, "the insane, and the devils which were supposed to possess them, were chained in madhouses, places even worse than the prisons of those days. There they remained poorly sheltered, scantily fed and unclothed to lie in their own excreta until they died of neglect and exposure. The only treatment they received was an occasional beating when their cries became annoying."

In non-Christian countries during medieval times the care of the insane was much better. In Arabia they were treated kindly and were kept in asylums where their Oriental love of hearing stories was used to keep them quiet.

It was during the Middle Ages that institutionalization of mental patients was inaugurated. Likewise a new impetus to the humane treatment of the insane resulted from the efforts of Philippe Pinel.

INSTITUTIONS

European

The earliest insane asylums in the northern countries were St. Mary of Bethlehem or "Bedlam" in London (1547), the Julusspital at Wurtzburg (1567), St. Lukes in London (1751), the Quaker or Country Asylum near York (1792), and the Narrenthurm or "Lunatics Tower" in Vienna (1784).

During the eighteenth century Bedlam was one of the "sights" of London and the public were allowed to view the insane like animals in a menagerie on payment of a small fee. Samuel Johnson and Boswell visited Bedlam and Steele took three school boys to see "the lions, the Tombs, Bedlam and other places which are entertainment to raw minds, because they strike forcibly on the imagination." (4,5)

It is stated that the conditions in Bedlam fully justified the significance which the word "bedlam" acquired.

The "open door" system was practiced at Bedlam. That is, the patients, after they had recovered from their primary attack, were allowed to go out wearing a plate on their arm which indicated that they had been in Bedlam for a time. John Aurbrey wrote, "Till the breaking out of the Civil War, Tom of Bedlams did travel about the country---they had on their left arm an armilla of

tin about four inches long; they could not get it off. They wore about their necks a great horn of an ox in a string or baudry which when they came to a house for alms they did wind, and they did put the drink given them into the horn whereto they did put the stopple." Perhaps Edgar in Shakespeares "King Lear" refers to this custom of drinking from the horn when he says: "Poor Tom thy horn is dry." These Bedlamers, as they were called, were cared for more sympathetically than while they were inmates of the hospital. In fact, they were cared for so well by the people that "sturdy vagrants", tramps as we would call them, would steal these plates or obtain possession of them after the death of the wearer and use them for imposition upon the people.(4,5,7)

However, the welfare of those confined within the various asylums was less fortunate. Hospital management was deplorable and living conditions were even worse. Lunatics Tower, where as in ancient Bedlam, visitors came to be amused at the antics of the inmates, was described in 1815 as a "fanciful, four story edifice having the external appearance of a large round tower, but consisting on the inside of a hollow circle in the center of which a quadrangular building arose joined to the circle by each of its corners. The enclosed structure

afforded residence for the keepers and surgeons. The circular part contained three hundred patients."(5) The patients were either chained or caged when housed or if harmless were allowed to run at large, the "wizards and warlocks" of Scotland. Lunatics Tower was not closed until 1853.

Garrison states that until well into the nineteenth century insanity was regarded as not only incurable but as a disgrace rather than a misfortune. Heinroth (1818) even regarded it as a divine punishment for personal guilt of some kind. In the later asylums including those erected at Munich (1801), Sonnenstein (1811), Seigburg (1815) and Sachsenburg (1830) the "sad lot of the insane was that of Hogarths engraving and Kaulbachs celebrated drawing."(5)

Monkemollers researches on German psychiatry in the eighteenth century confirm what Reil wrote of German asylums in his "Rhapsodies" (1803) and go to show that the theoretic part of the science was nebulous philosophic speculation.

Little progress in therapy was made at this time. A medical book written at the time Bedlam was opened summarizes the accepted treatment of the insane--"I do advertyse every man which is madde or lunatyche or

frantyecke or demonyacke to be kept in safe garde in some close house or chamber where there is lytell light; and that he have a keeper the which the madde man do fear." (4,5)

During the seventeenth and eighteenth centuries the only cases treated were of the dangerous unmanageable or suicidal type and no hope of recovery was held out. There was an unconditional belief in the efficacy of drugs, and cases that failed to react were regarded as hopeless. Opium was prescribed for melancholia, camphor for excited states, and diaphoresis for pruritis. A mysterious power was ascribed to belladonna; if it failed, everything failed. Numerous other remedies including a mixture of honey and vinegar, a decoction of Quadenwurgel, tartarus tartaresatus, aqua benedicta Rolandi, and large quantites of lukewarm water were used. Numerous procedures as venesection of the forehead and both thumbs, a mustard plaster on the head, and clysters of Spanish fly were other resources. (5)

A melancholic woman was treated with a volley of oaths and a douche of cold water. Likewise marriage was recomanded as a cure. Purgatives and emetics were used to control violent patients, and if this failed they received many hard knocks with bolts and chains to

inspire their fear. The diet was of the cheapest consisting of soup, warm beer, a few vegetables and salad. There were some attempts of open-door treatment such as putting the patients to mind geese or sending them as harvest hands to Holland. On the whole the brutalities of earlier times were ameliorated but the insane were still treated harshly. They were dosed with drugs, bled excessively, locked up in cold, dark cells and restrained with chains. (5)

The Quaker Retreat, founded by William Tuke in 1794 at York, England, was the first attempt at humane treatment of the insane. (5) However, the first influential champion of more gentle treatment of the insane was Phillipe Pinel (1745-1836) a physician at the Hospital Bicetre of Paris. It is stated that his incentive was the death of a friend who had escaped from an asylum and had been killed in the forest by wolves. (4) On May 24, 1798 with the consent of the National Assembly Pinel struck off the chains from forty nine patients at Bicetre, as depicted in the painting of Tony Robert Fleury. He placed these patients under lenient physicians, provided wholesome food and sunlight, and did away with the abuses of drugging and blood letting to which they had been subjected. The patients improved and these procedures were gradually adopted by the other institutions. In 1856 the "Treatment of the Insane without Mechanical Restraints" by John Conolly was published.

INSTITUTIONS American

Prior to 1850 there were a few private insane asylums in the United States, but most insane patients were confined in county poor houses or prisons. Miss Dorothea Dix spread the ideas of Pinel widely in this country and was instrumental in establishing as many as thirty two state asylums. In 1894 Dr. Weir Mitchell pointed out the evils of political control and the absolute lack of scientific study of insanity in America. Until the advent of the twentieth century the charge that the insane asylums were not hospitals where the mentally ill were treated, but were sanatoria where they were kept was probably justifiable. (8)

Grimes (2) states that there are in the United States six hundred and thirty one hospitals and other institutions caring for the mentally ill and the mentally deficient. They have a total rated capacity of 427,343 and they report a total patient population of 445,867. They admitted a total of 147,621 patients and discharged 83,794; there were 34,089 others who died in the institutions. These 631 institutions employ the full daily service of 2,337 physicians, 7,339 nurses and 38,790 attendants, as well as several thousand other

workers in various capacities.

Of the 631 institutions, 351 are owned and controlled by governmental agencies including federal, state, county and city governments; the other 280 are owned and controlled by private agencies including churches, independent associations, partnerships and individuals.

Of the 351 publicly or governmentally controlled, 251 are state institutions, nearly all of them of huge proportions. They contain 85% of all mental patients now in institutions; they receive 69% of all patients admitted to institutions annually.

Grimes (2) reporting in 1933 states that ten new state hospitals have been built in the last five years and eighty three have added to their bed capacity in the last five years.

From the 631 institutions for mental patients it was learned by special questionnaires that their patient population actually exceeded their capacities by 18,524. While the total patient population of all hospitals and related institutions was 808,445, the total population of the mental group alone amounted to 445,867 or 55% of the whole. The table on the following page summarizes the findings of Grimes survey.

PUBLIC INSTITUTIONS

	No. Hosp.	Rated Cap.	Av. Census	Excess	Admis.	Disch.	Deaths	In- crease
STATE	254	-	-	-	-	-	-	-
Insane	174	276436	299324	22888	88,589	46362	25781	16446
F. Minded	65	65699	65944	245	11,446	4035	1594	5817
Epileptic	11	10105	10060	-	2,047	591	587	869
Drug	1	122	85	-	149	33	1	115
CITY & CO.	76	35867	36871	1004	13,055	7532	3944	1579
FEDERAL VET. ADMIN.	20	14489	12370	-	6,293	4586	406	1371
FEDERAL INSTITUT.	4	4472	5309	837	1007	458	238	311
TOTAL GOVT.	351	407160	429963	24974	122586	63547	32551	26508
TOTAL NON GOVT.	280	20183	15904	*	25035	20247	1538	3256

PRIVATE INSTITUTIONS

PRIVATE ENDOWED	12	2,382	2,193	-	3,004	2,543	212	249
PRIVATE SANATORIUM	156	11,583	8,864	*	18,279	14,948	1,102	2229
PRIVATE HOMES	76	2,511	1,759	-	2,031	1,597	149	285
PRIVATE SCHOOLS	27	3,311	2,884	-	334	165	70	101
PV. INST. EPIL.	3	237	156	-	4	8	2	-
PV. INST. DRUG	6	159	48	-	1,383	986	3	392
TOTAL NON GOVT.	280	20,183	15,904	-	25,035	20,247	1538	3256
GRAND TOTAL	631	427343	445867	18524	147621	83,794	34089	29764

PUBLIC INSTITUTIONS							
	Pts./ Dr.	Res. Drs.	Reg. Nurses	Pts./ Nurse	Attend.	Pts. /At.	Av. Cost
STATE							.93
Insane	228.0	1,313	1,873	160	23,581	13	.93
F.Minded	334.0	198	120	550	4,683	14	
Epileptic	209.0	48	38	265	769	13	
Drug	425.0	2	2	42	21	4	
CITY & CO.	338.0	109	208	175	3,232	11	
FEDERAL VET.ADMIN.	43.0	237	636	19	2,161	6	274
FEDERAL INSTITUT.	166.0	32	28	190	791	7	
TOTAL GOVT.	222.0	1,937	2,905	148	35,238	12.2	

PRIVATE INSTITUTIONS							
PRIVATE ENDOWED	20.3	108	408	5.4	569	3.8	
PRIVATE SANATORIUM	34.6	256	530	16.7	2,432	3.6	700
PRIVATE HOMES	87.9	20	128	13.7	266	6.6	300
PRIVATE SCHOOLS	288.4	10	29	99.4	267	10.8	
PV. INST. EPILE.	156.0	1	2	78.0	9	17.3	
PV. INST. DRUG	9.6	5	9	5.3	9	5.3	
TOTAL NON GOVT.	39.8	400	1,106	14.4	3,558	4.4	
GRAND TOTAL	100.8	2,337	4,011	111.1	38,790	11.6	

*Average cost per patient per day

ONE (THE AVERAGE) OF THE 122 STATE
HOSPITALS PREVIOUSLY MENTIONED WITH
A PATIENT POPULATION OF 1,875

ADMITS 582 PATIENTS

DISCHARGES 310 ANNUALLY

194 ARE RECOVERED OR IMPROVED

THE NINE PRIVATE ENDOWED HOSPITALS PREVIOUSLY
MENTIONED WITH A PATIENT POPULATION ONLY 175
IN EXCESS OF THIS ONE STATE HOSPITAL

ADMITS 2,074 PATIENTS

DISCHARGE 2,062 PATIENTS

1,181 ARE RECOVERED
OR IMPROVED

Read and Nerancy state that an adequate professional staff consists of at least one physician per every one hundred fifty patients; one registered nurse per every hundred patients; and a nurse or attendant per every ninety eight patients. (9)

The criticism has been made that the patient, already retreating from reality, is even more isolated from reality by reason of institutionalization and separation from community life. (10) Likewise it is said that the patient is taken from an environment in which he was unable to adjust and placed in one adjusted to his reduced powers of adaption only to be returned, upon recovery, to the same environment, no better equipped to cope with his surroundings than he was upon commitment to the institution.

While it is true that the individual is separated from an environment in which he has failed to adjust and is placed in one which is plastic in its various degrees of simplification to fit his reduced powers of adaption, the majority of institutions have adopted programs of education and reeducation.

The Old Hartford Retreat in Pennsylvania is a pioneer in this respect. In 1931 an attempt was made to convert this institution into an educational center

with as normal an environment as possible. In accordance with this, anything smacking of institutionalization was eliminated. Attention was concentrated on personnel. Attendants were supplemented by psychiatric aids who were required to have at least a high school education. Educational measures were instituted. At the present time a daily program which requires regular hours of study is planned for each patient. As his condition improves he is provided with the opportunity of attending one of the local business schools. He is instructed in courses that will help him become more efficient in his vocation or that start his training and interest in a new vocation more suitable to his personality. These courses are supplied by some of the leading universities of the country. Extension courses in business, economics, finances, insurance and government are offered in which the patient is responsible for his work directly to the university. Art classes and classes in costume designing and horticulture are also offered. A good library, with recent books in literature, music, history and with current periodicals, is maintained and its use is encouraged.

Physical education courses are maintained and training in golf, swimming, squash and badminton is offered. Class instruction is provided for those who have not

learned to play bridge or to dance. Evenings are devoted to social functions and amusements including up to date moving pictures, plays, concerts, dances and bridge parties are provided.

Separated from the main hospital building a small street of shops, including a beauty parlor and book shop, has been erected. A dress shop is maintained and a fashion show is held at the beginning of each season. Patients must make their own selection and purchases thus doing away with "dispensing". (10)

In concluding this section of the institutional care of the insane it is appropriate that the applicable parts of the program sponsored by the National Committee for Mental Hygiene be outlined. The Committee tenders the following suggestions:

B. "Treatment

1. Provision for earlier diagnosis and treatment

"Out patient departments for mental cases in connection with hospitals for mental diseases and general hospitals and independent of either of these agencies

Provision for incipient and emergency cases in psychopathic wards of general hospitals

A psychiatric hospital in each of the fifty United States cities of more than 100,000 population; such hospitals to be the centers of practical work in prevention and social service as well as for efficient treatment

2. Improvements in methods of admission and commitment
 - Transfer of the responsibility for the care of patients pending commitment from overseers of the poor and police officials to physicians
 - Improvement in the legal steps necessary for admission to hospitals especially elimination of court measures which often imperil patients chances for recovery
 - Extension of the use of the "emergency" and "voluntary" commitments
3. State Systems for the public care of the insane and mentally defective
 - Establishment of complete state care and state supervision of private institutions, under strong central administration
 - Elimination of politics from state institutions; all appointments and promotions under strict civil service control
 - Establishment of after-care and social service work under the direction or with the full cooperation of state institutions
4. Institutional provisions
 - Sanatoriums for early cases of mental disorders and especially for psychoneuroses
 - Hospitals of moderate size in cities with facilities for active treatment of acute cases
 - Colonies in the country for more chronic cases where patients may be treated in small groups under attractive and home like surroundings
5. Special features of treatment
 - Increased number of physicians in state hospitals and especially provision for training young physicians who enter this work
 - Encouragement of research in many fields."

(11)

IRRITATIVE THERAPY

"Canst thou not minister to a mind diseas'd;
Pluck from the memory a rooted sorrow;
Raze out the written troubles of the brain;
And with some sweet oblivious antidote
Cleanse the stuff'd bosom of that perilous stuff
Which weighs upon the heart?"

Shakespeare

Metrazol

Metrazol, according to American terminology, or cardiazol, according to European terminology, and camphor are the two irritative or convulsive drugs to be considered in this section.

Notkin, in 1929 commented on the relative absence of convulsive episodes in schizophrenia and in manic-depressive psychosis.(12) Meduna believing that a biologic antagonism existed between epilepsy and schizophrenia, attempted to treat the later by reproducing epileptiform convulsions. In 1935 he utilized metrazol for this purpose.(13)

In addition to the treatment of schizophrenia, metrazol has recently been utilized in the treatment of depressive psychosis, including manic-depressive and involutional types, and in the treatment of the psychoneurosis.(14,15,16,17)

Meduna (13) and Friedman (18,19), Kennedy (20), Sorger (21), Reese (22,27) and numerous other authors have noticed that the catatonic type of schizophrenia which is relatively refractile to insulin therapy shows the greatest tendency to remit with metrazol therapy. This is closely followed by the paranoid type of schizophrenia. Some authors, in fact, maintain that the psychosis with a predominant picture of motor phenomena is to be handled with convulsive therapy (metrazol) while the psychosis demonstrating mainly psychic phenomena (hallucinations, delusions) is to be treated with insulin. This latter supposition is subject to dispute.

Friedman and Meduna (13, 18, 19) classify contraindications as absolute and relative. Absolute contraindications of this therapy include; (a) evidence of cardiovascular disease, (b) acute febrile infections, (c) menstruation, (d) pregnancy, (e) severe anemia or cachexia, and (f) any abnormality of the blood or urinary constituents. Relative contraindications include; (a) exophthalmic goiter, (b) history of severe intracranial injury, (c) seropositive syphilis, (d) latent tuberculosis, (e) confinement to bed for one year before treatment is undertaken. (19)

In relation to cardiovascular disease it is interesting to note that Drs. Bennett and Wright (16) report that in eighteen patients receiving metrazol therapy the original electrocardiographic record was unchanged by the convulsive therapy.

Various modifications of metrazol treatment have been described in the literature, but the technique is fundamentally the same. Friedman (18) divides the treatment into two parts. In part A the patient is given a thorough physical examination and a complete laboratory examination. During this time he is placed on an alkaline diet sufficient in calories, vitamins, and bulk. He is given sodium bicarbonate (1.3 G) three times daily. Fluid intake is set at a minimum of two liters per day. The urine is tested daily for the first five days and following this is tested twice a week for alkalinity throughout the treatment. Part B consists of the actual metrazol regime.

A ten per cent aqueous solution of metrazol is used intravenously, as veins tend to become sclerosed after a few injections of the twenty per cent solution. The solution is stable and does not deteriorate with time. (17) A twenty per cent solution does not increase the incidence of convulsions. (22,27) The initial dose of metrazol varies between two and five cc. and therapy

is continued every other day. Finkleman et al (23)

have given a good summary of the treatment as follows:

"The treatment is given in the morning when the patients stomach is empty. The dose is the smallest amount of the drug that will produce a typical convulsive seizure. Our first dose is ranged from two to five cc. of the ten per cent solution. As a rule we administered about one cc. for about each thirty pounds of body weight but not over five cc. for the first dose. This dose usually produced a convulsion. When the convulsive dose was reached it was maintained until we failed to get a reaction. In such cases the treatment was repeated the next day the dose being increased by one cc. For patients with a longer duration of the psychosis the dose of the drug had to be repeated more often than for others. The treatment was administered two or three times a week."

Friedman (18) places the initial dose of metrazol at five cc. Subsequent doses are increased at the rate of one cc. every injection irregardless of whether or not the convulsions occur. He sets the maximum dose at sixteen cc.

When the dose is insufficient to produce a complete convulsion a minimal reaction consisting of mental confusion and a few myoclonic movements occur. Friedman (18) terms these reactions "petit mal reactions". He observes that the patient undergoes a restless type of gross twitching for one or two seconds and that this is immediately followed by a period of intensely vivid hallucinatory reactions lasting for as long as two hours.

With a still smaller dose there is no reaction except pallor, cough and anxious facial expression.

Reese (22) states that such an attack, simulating petit mal, creates a fear complex with a sensation of impending death. Repeated failures to produce convulsions, and thus amnesia, develop reactions which soon result in objective aversion, opposition and refusal to accept this therapy. According to Cook and Walters (24) the symptoms of the psychosis may be more pronounced than before the injection. Friedman (19) reached the same conclusion after a number of patients, who were progressing nicely, suddenly had relapses after subconvulsive or "petit mal" doses.

Friedman (19) therefore uses the following technic: The initial dose of metrazol is the same as mentioned above. If a convulsion does not take place within one minute, another injection of one cc. more than the original amount is given. If again a seizure does not take place, the treatment is taken up the following morning beginning with one cc. more than the last dose. This procedure is repeated until a convulsion occurs. He finds that even in cases of the most resistive type, a convulsion will occur on the third or fourth day of the treatment at most. As high as forty six cc. has been

given by him in a single period in increments of 16 plus 16 plus 14 cc. without deleterious effects on the cardiovascular system.

Low et al do not hesitate to repeat the injection after about thirty minutes have elapsed. (17)

Reese states that in order to avoid the objections and psychic irritations in metrazol failures he had adopted the recommendation of Georgi. That is, insulin in shock producing amounts is given, and after two hours of hypoglycemia the patient is given a convulsion with metrazol. The convulsions terminate the patients' hypoglycemic state and he is able to take the sugar water.

The reaction to metrazol as described by Cook and Walter (24), Friedman (18), Low (17), Finkleman (14), and Himwich (25), takes place in the following manner. Within two to five seconds after the intravenous administration of metrazol there is a blepharospasm and mouth twitching and the patient coughs. Five seconds later, ten seconds after the injection, marked pallor of the face occurs. From eight to twenty seconds after the injection a tonic convulsion begins in the face, shoulders and arms. This lasts from two to ten seconds. This is followed in about fifteen seconds, ten to thirty seconds after the injection, by a clonic phase with the head retracted and the back arched. The wrists and legs

are contracted in extension and the extremities may assume various postures. The clonic phase lasts from five to thirty seconds and is followed by another tonic phase, eighteen to forty seconds after the injection, which begins in the fingers and then spreads to involve the entire body. These movements are rapid at first and then gradually become less frequent, ceasing in from twenty five to fifty five seconds. During the tonic phase the face is flushed. As the clonic phase sets in, cyanosis develops and continues throughout the clonic spasm. Coincident with the cyanosis the flush turns to pallor which is usually followed by a period of apnoea lasting a few seconds. Within a few more seconds the patient resumes breathing. At this time according to Himwich et al (52) the amount of oxygen available for brain metabolism is reduced and this may be an important factor in explaining the benefit obtained from the convulsive seizure. The entire spasm is over in about sixty or seventy seconds. The pupils are nearly always dilated throughout the reaction and the eyes often show extreme lateral deviation. Brief after twitches may occur as late as a minute or two after the paroxysm. Occasionally micturation occurs. After the convulsion patients frequently fall asleep for a few minutes or in some cases for several hours. Others display great motor restlessness without any well defined

pattern. Usually patients remember only the injection and the feeling of anxiety and have amnesia for the rest of the seizure. (23) It is unwise for one patient to see another during the convulsion and treatment should be given individually.

The treatment is continued until the patient shows a remission. As a general rule, it has been found helpful to induce a minimum of about twenty five reactions of "grand mal" type before abandoning treatment in cases of failure to respond. Patients who respond should be treated until the maximum improvement or remission can be noted. Then, it is believed, three or four additional seizures should be induced to prevent the possibility of relapse. In the event a relapse occurs, therapy is reinstituted until improvement is again noted.

Metrazol is not used to the exclusion of other recognized means of treatment. The various occupational, recreational and reeducational routines are instituted in coordination with metrazol therapy. Psychotherapeutic advances should not be forced on the patient; rather these advances should lag behind the progress of the patient. Friedman and Meduna (19) have the patient come to their offices for interviews at the termination of every four or five seizures. A full or complete remission cannot be said to have occurred unless there is complete insight and until the patient has satisfactorily

worked out and assumed a critical attitude toward his pathologic experiences.

The occurrence of three or four convulsions are not regarded as harmful. However if they tend to continue beyond this number or tend to merge, intervention is necessary. These convulsions are easily controlled by the intravenous use of the standard barbiturates, hypodermic administration of morphine and atropine, rectal administration of ether or avertin with amylene hydrate, or inhalation of ether, chloroform or ethyl chloride. (21)

Complications of this therapy may be classified as "mechanical and inflammatory". Meduna (13) lists no complications directly referable to the drug action in over a thousand cases. During the course of a convulsive seizure mechanical injuries including dislocation or fracture of the jaw, arms or legs may occur unless prevented. It is inadvisable to prevent all movement, but abduction of the limbs should be prevented. Injury to the tongue may be prevented by placing a soft rubber wedge between the teeth during the tonic phase when the mouth is open. (23) Low et al report that nausea and vomiting is not uncommon after the first convulsion,

but that these disappear rapidly as treatment progresses. Friedman and Meduna (19) include "inflammatory complications". These consist of pulmonary abscesses, activations of latent pulmonary tuberculosis, acute (myocardial) reactions. They have computed the incidence of complications in a total of 2,937 American and European patients as 2.2%, both mechanical and inflammatory complications having equal values. Mortality in this series of cases was 0.29%.

In schizophrenia, the results of this therapy are very encouraging. According to a number of statistical workers it has been found that the rate of spontaneous remission of schizophrenic patients varies between four and twelve per cent. (19) Finkleman (23) found that the rate of remission with metrazol therapy was almost inversely proportional to the duration of the psychosis. When the psychosis had lasted more than three years there was only a slight possibility of remission. American workers have classified cases of schizophrenia of less than six months duration as acute, cases of less than twelve months duration as subacute, and cases of two years duration or more as chronic. Meduna (13) Friedman (18) Kennedy (20) and Sorger (21)

report that more complete remissions are obtained in the acute cases of schizophrenia. Meduna (13) reports a remission rate of 82% in the acute cases. Low et al (17) report their percentage of recoveries as follows: acute cases, 84.6%, subacute cases, 65.6%, and chronic cases 28.6% Sarger and Hoffmans results compare very favorably, 76.3%, 53.8%, and 26.5% respectively. Friedman and Meduna (19) in a review of the statistics of 1,465 American cases treated in thirty seven hospitals report a remission of 60.95% in acute cases of schizophrenia, a remission of 38.83% in subacute cases of schizophrenia, and a remission of 8.36% in the chronic cases of schizophrenia. European statistics closely agree with these figures.

Young and Young (14) state that while the therapeutic use of convulsions induced by metrazol has been to date largely confined to the schizophrenic group, there is no reason to believe that its efficacy should be restricted to any special type of personality dysfunction. They have applied this form of therapy to the affective psychosis (depressions). Twenty one such cases were treated and complete restoration was obtained in twelve of these cases. Six other cases were markedly improved by the treatment. Two others were improved and gradually rec-

vered. One patient showed no improvement. These were selected cases. Bennett (16) reports twenty one patients with affective psychosis who all showed improvement within two weeks after convulsive shock therapy was instituted. He states that one relapsed to the manic state. His cases consisted of manic-depressive, reactive and involutinal types of psychoses. Low et al (17) have treated a group of sixteen patients with manic-depressive psychosis. Of these five had the manic, nine the depressed and two the involutinal types of psychosis. In this group were six patients whose present attack had lasted more than two years. Five of this group of six recovered. From these results Low et al infer that the rate of recovery for manic-depressive psychosis does not depend on the duration of the attack. These writers report a case of anxiety neurosis of five years duration with remission by metrazol. In a case of hypochondriasis of five years duration four metrazol convulsions produced remission. They report a case of "shell shock" neurosis of eight years duration with remission following four metrazol convulsions.

The number of available reports relative to the mode of action of metrazol is limited. At the present time no conclusion has been reached as to its exact mode of

action in removing or ameliorating the symptoms of mental disease. Clinical, laboratory and autopsy findings have been of little assistance. Electro-encephalograms are of value especially with reference to negative findings.

Cook and Walter (24) report that two different reactions are recorded on the electro-encephalogram, following the intravenous injection of metrazol. One type occurs when the injections fail to produce a convulsion, and the other is obtained when a convulsion ensues.

When an injection fails to produce a convulsion, no change is seen in the electro-encephalogram at first. Then small waves, having a frequency of six per second, appear in all leads and involve all areas of the cortex. They increase gradually in size during the first minute and remain for a number of hours. The electro-encephalogram does not resemble in any way that found in cases of petit mal for this condition is characterized by a focal discharge at a frequency of three per second.

When an injection is successful in producing a convulsion the electro-encephalogram starts in the same way after a latency of a few seconds. Although the waves appear in all areas they grow more rapidly and have a

slightly lower frequency. Fifteen seconds following the injection there is an abrupt increase in the size and a drop in the frequency of the waves in the frontal region. This may occur on either or on both sides. At this moment the tonic phase of the convulsion begins. The area involved by large slow waves increases in size and spreads over the greater part of the cortex. As the convulsion passes into the clonic stage, the discharge becomes more staccato in rhythm and then suddenly ceases. about one or one and one half minutes following the injection, The electro-encephalogram is now abnormally quiet, no waves of any sort being seen, and the patient is completely relaxed and flaccid. With the return of consciousness the normal small random potentials reappear and thirty minutes later neither the "patient or electro-encephalogram show any trace of the storm which has agitated them." The striking feature of this type of reaction is the sudden increase in potential and the drop in frequency in the area of the superior frontal gyrus.

(24)

As small doses of metrazol produce an abnormal discharge in all areas, these authors state that it cannot be supposed that metrazol has an entirely selective action on one part of the cortex. They state, "it may

be that when a certain concentration of cardiazol is reached, this frontal area becomes unstable and acts as detonator for the rest of the cortex which is already poisoned by the drug." They mention that it should be remembered that the electrical threshold for convulsive movements has been found to be lower in this area than in other parts of the brain. Another possibility is that this area by reason of its anatomical connections is first to signal the onset of an abnormal condition in some subcortical center. (24)

Low et al (17) find the following values ten minutes after the convulsions; (a) the blood pressure which was usually higher to begin with rose from about 146 mm. Hg. to about 198 mm. Hg. , (b) the pulse and respiration were likewise increased, (c) the mean value of the pH fell from about 7.35 to 7.17, (d) carbon dioxide volume percent fell from normals of about 10 mg.% to about 8.75 mg.%, (f) fasting dextrose values rose from about thirty to sixty percent and remained in excess of preparoxysmal levels for at least three hours. Sorger and Hofmann (17) also reported an increase in dextrose content of the blood immediately following the convulsion, attaining its greatest height about thirty minutes later. This returned to normal within a

few hours. Meduna (13) and Kennedy (20) find that during the three hour period following the convulsion there is a decrease in the urinary acidity, a reduction in ammonia content and a considerable reduction in the urinary chloride.

Only four fatal cases have been reported in the literature to date. In these deaths associated with metrazol therapy preexisting pathologic conditions were present including aortic disease, hypernephroma and goiter, and pulmonary embolism and pelvic thrombophlebitis. Hayman and Brady report a case of a man of twenty four years of age, whose physical and laboratory data was negative, who suddenly died after the sixth treatment following the injection of 5 cc. of metrazol. Morbid anatomy revealed marked congestion of all of the organs and a preexistent endocarditis with no other distinct lesion. They state that the probable cause of death was "the toxic effect of a pharmacologic agent on a pathologically impaired heart." (24,25)

Friedman (18) believes it is possible to think theoretically of schizophrenia as a result of general sluggishness of body metabolism and that in schizophrenia there might be, again theoretically, a physiological barrier to certain thought processes which would tend

to become more impenetrable as the disease progressed. In his opinion the benefit from metrazol therapy is brought about by a stimulation or irritation of the whole central nervous system to the extent that these so called barriers were broken down, allowing proper thought processes to be carried on. The action of the alkalization is that of increasing the irritative background so that tolerance to the convulsant drugs is lowered and the action of the latter is more rapid.

Camphor

Camphor in the form of a twenty five percent oily solution given intramuscularly is another type of the irritative therapy of the psychoses. The indications and contraindications for the use of camphor as a convulsive drug are essentially those of irritative drugs in general. These phases have been discussed with relation to the use of metrazol.

A freshly prepared sterile solution of camphor is injected twice daily only after the urine has been alkaline for two days. The initial dose is placed at 16 cc. (4.0 G) and the subsequent doses are increased at the rate of 4 cc. per day. When convulsions occur at any given dose, the injection is omitted the following day, and the next dose is the same as the convulsant dose. If convulsions do not occur after four injections, three or four days are allowed to elapse before the injections are resumed. They are then resumed at an increase of 4 cc. to 6 cc. The maximum dose of camphor is set at 56 cc. (14 G). (18) Meduna determined that the convulsive dose of camphor varies not only in the different patients but also in the same patient at different times.

Convulsions occur from fifteen minutes to three hours after the injection, and as high as six individual

convulsions have been noted. The convulsions are manifested over a longer period of time than are those occurring with metrazol, and usually occur without any warning. (18)

Irregardless of whether convulsions occur Friedman noted that there is a "deliri-form or twilight state somewhat similar to an individual mildly under the influence of alcohol or camphor." He states that the patients walk about as though dazed and that reactivity to vivid and painful hallucinations, chiefly of the somatic is frequently noted. This reactivity differs in many ways from the reactivity and the content of the hallucinations noted before the treatment was started. According to Friedman this difference was noticeably significant in that the patient registered concern and anxiety about the hallucination. Occasionally the patient would become assaultive and destructive. These reactions to camphor may remain for as long as ten days following the last injection. Patients, upon recovery, relate that there is only partial amnesia. (18)

The immediate obnoxious effects of camphor are nausea, emesis, a mild form of ataxia and infrequent complaints malaise and pains in the extremities. Two cases of bilateral subcutaneous abscesses in the gluteal

region resulting from camphor injections have been reported.

SHOCK THERAPY

Insulin Shock

Insulin shock was introduced by Sakel at Professor Potzels' clinic in Vienna in October, 1933, as a new form of therapy in mental disease. Prior to this time insulin, in smaller amounts, had been used in the treatment of the psychoses. Cowie, Parsons and Raphael tried a combination of from two to ten units of insulin with glucose in cases of depression without resulting signs of clinical improvement. They did note that the prolonged dextrose utilization curve was changed by insulin to a normal curve. Targowla and Lamache in 1926 and Puca in 1927 successfully used daily doses of up to forty five units of insulin combined with glucose to improve the appetite and nutrition of patients. They noted the disappearance in the course of treatment of the motor symptoms of a subject with catatonic stupor. Appel, Farr, and Marshall in 1928 used insulin in the treatment of thirty three patients with psychoses who presented intractable malnutrition. They noted a definite improvement in the mental status in twenty per cent of these patients. Paul Schmidt in 1928 was the first to deliberately use insulin for its therapeutic effect on the psychoses as such. He

administered from sixty to eighty units of insulin a day and noted that stuporous patients grew active and that agitated patients grew calm. All of these authors and numerous others used carbohydrates in conjunction with insulin and strenuously avoided hypoglycemic shock. (26, 27)

The application of insulin shock in the treatment of schizophrenia developed purely empirically as an outgrowth of Sakel's original employment of insulin in the management of the withdrawal symptoms in morphine addicts. In connection with this Sakel observed that the occasionally unavoidable hypoglycemic states which developed in these patients in spite of the fact that the administration of the insulin was accompanied by the simultaneous administration of carbohydrates had a distinctly quieting effect on motor excitements. He then extended the application of this treatment to various forms of schizophrenic disorders and made the significant discovery that the insulin shock proved to be of benefit in the treatment of schizophrenia. (26, 28, 29, 30)

Since its introduction in Vienna in 1933 it has been employed in public mental hospitals in Switzerland, in the Netherlands, in Poland and in isolated German clinics, in the Moscow Psychiatric Clinic and in the United States.

With regard to indications, this form of therapy has

been limited almost exclusively to schizophrenic disorders. Reese (22) states that all patients with schizophrenic psychoses should be submitted to insulin therapy before attempting other forms of therapy. Of these patients he states that patients with early paranoid and catatonic disease offer a more favorable prognosis with insulin whereas stuporous catatonic and depressed hebephrenic subjects respond better to metrazol. Frostig (31) also believe the treatment to be worth while in cases of incipient paranoid development. It is not unlikely that, in the future, this form of therapy will be extended to other forms of mental disease.

Knowledge of contraindications for the treatment is still incomplete. Frostig (31) excludes all psychotic patients with severe physical symptoms from treatment. Reese and Vander Veer state that coronary disease, severe pulmonary disorders and severe cardiac disorders are absolute contraindications. Experience has shown that the response to insulin treatment stands in inverse ratio to the duration of the illness. Reese and Vander Veer do not apply this treatment to patients over forty years of age. (32)

Regular insulin is used in this type of therapy. Reese and Vander Veer experimenting with protamine zinc

insulin report that it is almost impossible to produce comatose shock even with large doses of this compound and with blood sugar levels as low as 18 to 20 mg. Likewise the effect is inconstant. They therefore abandoned this method of procedure after a month and returned to the use of regular insulin. (33)

The technique requires that the patient be given increasing doses of insulin until the so called shock dose is reached. A shock dose is defined as that amount of insulin which in any individual produces deep coma with areflexia within four or five hours after one injection. (30) The term "coma" should be associated with the absence of the corneal reflex or at least with the presence of a Babinski. The duration and depth of the coma vary with the dose of insulin and with the sensitivity of the patient; the reaction is dependent partly on the endocrine balance of the patient and partly on metabolic conditions and other unknown factors. (31) Response to any one dose varies from individual to individual and in the same individual at different times. The size of the shock dose also varies considerably in different individuals and may be anything from 15 to 450 units. (26, 28, 29, 30, 31, 32) Reese states that hydration or dehydration, alkalization or acidism, administration of oxygen or atropine have not influenced

materially clinical symptoms or phasic course of insulin induced hypoglycemia. (22) The treatment has been divided into four stages by Sakel. Phase I is the introductory phase; phase II is the phase of severe shock; phase III is the phase of rest; and phase IV is the terminal phase. (29, 31) The intensity and duration of each phase is strictly graduated with the requirements of the individual case.

Phase I consists of graduated intramuscular injections of regular insulin. Wortis (34) suggests that the patient be prophylactically digitalized for six to eight days during this phase. The size of the initial dose of insulin used varies with different experimenters. The aphorism, "experience is fallacious and judgment difficult" is nowhere more apropos than in connection with the variability of the individual's response to insulin. In Sakel's original report the initial dose varied from between twelve to twenty units. This initial dose was then increased by five to ten units six days a week followed by the so called rest day when the treatment is omitted. This was given on an empty stomach between seven and seven thirty in the morning. The patient was then kept in bed and about four or five hours later was given from 150 to 200 grams of sugar in tea, water or milk by mouth and

shortly afterward his regular mid day meal. During the rest of the day the patient was permitted to carry on the usual hospital routine unless prevented from doing so by certain special conditions. In case of marked excitement another injection of the same dose of insulin was administered at two o'clock in the afternoon and this was followed by the neutralizing carbohydrate within two hours. (29)

More recently Sakel has advocated an initial dose of from between fifteen and fifty units of insulin, and a daily increase of from five to twenty units. Reese and Vander Veer, after the findings for the blood and urine have been checked for several days and the sugar tolerance and reactivity to insulin are established for the patient selected, submit their patients to an initial dose of 60 units of insulin. The daily increase ranges from ten to thirty units. (30, 32). Frostig (31) uses an initial dose of from ten to twenty units of insulin with a daily increase of from five to twenty units. He warns against too rapid an increase in the doses, since symptoms of collapse or of protracted shock may ensue. Just how far this first phase has to be carried until the second phase is reached is subject to great variation. Apart from the well know fact of individual differences in sensitivity to insulin, the differences in the symptoms which appear in the hypo-

glycemic state seem to determine the degree of reactivity of insulin antagonists (adrenalin, pituitrin) which affects in turn the progress of the hypoglycemic state. Thus in cases with considerable muscular irritability there is probably a greater tendency towards an adrenalin neutralization of the effects of insulin. According to Sakel, old cases of schizophrenia seem to be more resistive to the influence of insulin than recent cases. (29) Frostig (31) reports that insulin shock may start, in some cases, with as little as twenty units of insulin. Katzenelbogen et al (35) report that shock producing doses in their series of cases varied from 25 to 200 units of insulin. Wortis et al (36) report shock dosages varying from 40 to 165 units of insulin. Reese and Vander Veer (33) state that they were able to obtain deep comatose hypoglycemic shock with from 70 to 220 units of insulin. Gluck (29) observed one patient who failed to show the slightest physical or psychic signs of hypoglycemia after repeated injections of as many as 240 units of insulin. Vander Veer and Reese (37) report that there is no correlation between constitutional (weight, height etc.) or psychic factors and the size of the shock producing dose.

The precise point of transition from phase I to phase II is to a large extent arbitrarily determined.

Phase II is the so called shock phase, the most important stage in the treatment. In practice this stage is assumed to have been reached when the dosage of insulin produces a degree of coma which no longer enables the patient to drink the sugar solution voluntarily and nasal tube feeding has to be resorted to, or irrespective of the degree of coma and other manifestations of deep hypoglycemic state the patient is threatened with a convulsive seizure. (29,31) As this stage is approached, the patients should be prophylactically tubed before each treatment. Patients may be permitted fluids during the shock, and throughout this phase laxatives and sedatives are prescribed as needed. Special attention should be concentrated on preventing the backflow of saliva. (26) It is in this phase of the treatment that one must be ready for emergency intervention, either through the intravenous administration of a 33 to 40% glucose solution (at times as much as 150 to 180 cc. is necessary before the hypoglycemia is neutralized) or in addition also through the hypodermic administration of adrenalin and at times of cardiac and respiratory stimulants. The nasal administration of an adequate amount of sugar must nevertheless also be carried out. (26,35,36)

Once the shock dose has been determined for any patient, the amount is usually adhered to for some time; changes are required from time to time by variations in the patients activity. Moreover,, during the course of treatment sensitivity to insulin usually manifests itself, requiring frequent reduction in the shock dose. (26,29, 30,31,32,34,35,36,37) Cases have been reported where it was possible to reduce the insulin from 160 to 30 units, deep shock being produced with both doses; and from 80 to 25 units. (32) Treatment is continued for from five to six days a week until it is apparent that no further progress can be made. Frostig (31) recommends that small doses of insulin (from 20 to 30 units) be given even on rest days in some cases to cover the carbohydrate requirements of the day. According to Reese (22) the total period of hypoglycemia should not exceed six hours. The lowest glycemia is reached from one to two hours after the injection and this corresponds to the critical physiologic danger zone, i.e. when hypoglycemic irritation phenomena begin to appear. (22,35) It is during this time that complications may occur which require immediate termination of the shock. These complications will be discussed later.

Termination of coma may be effected in four differ-

ent ways. In the lighter degrees of coma the patient can swallow, and two glasses of sugar and water, tea or egg-nog, containing ninety grams of sucrose to the glass, are sufficient to terminate the coma. As soon as full consciousness returns a meal rich in carbohydrate should be given. The second method consists of the administration of the sugar solution through the nasal tube. This is the method routinely used to terminate coma. In these two methods termination of the coma is usually attained from fifteen to forty five minutes following the administration of the sugar. If the patient is in deep coma, he may be brought to full consciousness in from one to five minutes by the intravenous injection of a fifty per cent solution of dextrose. Usually from 10 to 30 cc. is sufficient. This is the method of choice when quick interruption is necessary. It has the disadvantage of causing gradual venous thrombosis when used daily, and its use should always be followed by a physiological solution of sodium chloride. A final method of terminating shock is the intramuscular injection of from 1 to 2 cc. of a 1:1000, solution of epinephrine. This procedure is recommended especially for the termination of epileptiform shock. (26, 32, 37)

Phase III is merely a transition stage between

phases III and IV. It is really limited to a designation of the usual and the occasionally unavoidable rest periods in the treatment; that is the usual seventh day every week. After epileptic seizure the patient is usually allowed three days freedom of the treatment. (26)

Phase IV refers only to the cases in which the preceding treatment led to the desired result. That is, when the patient is recovered and when psychotic phenomena no longer occur in the course of hypoglycemia. In this phase the amount of insulin administered is reduced by from 20 to 40 units a day, and the carbohydrates are administered no later than two hours after the insulinization. (26,31)

In a recent article Vander Veer and Reese state that if improvement is to occur some indications are present within three or four weeks following the institution of the therapy. If from thirty to thirty five deep comas have not favorably modified the patient's conditions, the treatment is discontinued by them. (37) Young et al (14) concur in this opinion. Frostig (31) considers the maximum number of severe shocks to be fifty. If after this number of shocks the patient does not show signs of improvement he is then dismissed as "unimproved." He states that in cases in which no marked improvement has occurred but in which the prognosis seems

favorable, the maximum number of shocks may be extended. Reese considers sixty days the minimum for insulin treatment with almost ninety days for older disease. (22)

Sakel attempts to formulate more precise rules for the administration of this treatment in the paranoid, catatonic, and catatonic excitement types of schizophrenia. He believes that the hypoglycemia suppresses the momentarily most active part of the psyche and thus makes possible the emergence of the latent aspects of the psyche, which then supplants to a greater or less extent the acute existing manifestations, which have already been repressed by the insulin. According to him, before the stage of complete coma is reached, the hypoglycemia inhibits and delimits the existing (psychotic) state and converts it into the opposite. Thus a manic patient becomes depressed and a confused patient becomes lucid. He states that he has been able to observe in many, if not in all, cases that a hallucinated or delusional patient would manifest a brief period of complete lucidity just before falling into deep coma. The same patient, after the improvement has progressed far enough to enable him to behave quite normally when not in the hypoglycemic state will, during the shock, become acutely psychotic again for a brief period before sinking into deep coma. Sakel terms this the "activated psychosis". (26,30) This phenomena

has also been noted by other observers. (31,32,38) Sakel further refers to the strong tendency towards the fixation of the condition which exists at the time of the interruption of the hypoglycemia. In the main this refers to conditions of passivity and activity, and of excitement and calm. Thus the interruption of the shock in the case of an excited catatonic during a state of calm and passivity would tend to establish a similar condition also for the non hypoglycemic phases. Conversely, in the case of a stuporous patient the interruption of the shock during a stage of activity and excitement would tend to continue to activate the patient outside of his hypoglycemic state. He accordingly stresses the importance of determining the most advantageous moment for interrupting the shock. (26,30)

In the case of patients who are predominately stuporous, the hypoglycemia is interrupted at the first indications of activation either in the form of some release phenomenon or an excitement in order to establish a condition which is, as much as possible, in contrast to the existing stupor.

For those cases which are predominately paranoid in character the hypoglycemic state is permitted to reach a deep degree of coma and the shock is never interrupted during the manifestation of an activated psychosis. The

aim here is essentially as complete as possible a suppression of the existing psychotic state, and the favoring of as complete an amnesia as possible.

With regard to the catatonic excitements Sakel states that from the very beginning he and his associates were impressed with the fact that this type of patient did not respond as favorably as the others to the hypoglycemic state. He proceeds in treating this type of patient as in the others with from fifteen to twenty units, but he administers this from two to three times daily because of the need of quieting the excitement. The dose is increased daily by from five to ten units. When the patient quiets down, the hypoglycemia is induced only once daily and, during the early stages in the treatment, is terminated through the mere administration of food, later through the usual administration of sugar. After the shock dose is attained the most favorable point for interruption seems to be the moment of maximum somnolence and just before the patient sinks into a deep coma. (26)

In the course of phase I the clinical hypoglycemic manifestations begin to occur, usually with increasing intensity. These symptoms of hypoglycemia are dependent more upon the rapidity of the change in the concentration of the blood sugar rather than the actual amount of sugar

in the blood. Thus a patient whose blood sugar has been lowered gradually may have no symptoms whatsoever. The hypoglycemic reactions in schizophrenia are essentially similar to those observed in patients who are mentally normal. Subjectively the patients experience a certain sedative feeling, a pleasant feeling of warmth throughout the body, and slight paresthesias of the finger tips, palms of the hands and around the mouth. Occasionally they complain of a slight anxious, oppressed feeling around the heart, pounding of the heart and double vision. The only reaction during the first few days of therapy occurs about one hour after the injection and consists of sensations of hunger and light perspiration. On the second, third, and fourth days, the patient often does not react as much as he did on the first day. After this the extent of the reaction generally parallels the amount of insulin given. As the dose is increased, greater degrees of hypoglycemia are produced, and the patient falls into progressively deeper phases of insulin shock. The light perspiration proceeds to profuse diaphoresis and there is usually increased salivation of a peculiarly viscid type. During the fourth or fifth day of treatment somnolence, slurred speech, ataxia, confusion, diplopia and often euphoria are superimposed upon the previous reaction. Following

this some degree of purposeless psychomotor activity is added to the reaction. This occasionally reaches a stage of wild excitement. This stage of excitement is comparable to the state of confusion in mentally normal hypoglycemic patients. Some patients do not experience this stage of excitement but quietly pass into the stage of coma. Tremor may occur early in this stage. Later on motor excitement in the form of clonic twitchings of the musculature of the extremities, shoulder girdle, and face appear. As the shock dose is approached the sensation of hunger disappears its appearance being forestalled perhaps by the onset of the coma. (26,31,32,38,39,40) The beginning of shock is characterized by the appearance of motor disturbances, such as clonic spasms and epileptiform convulsions, and by loss of contact with the outside world.

Three types of shock, wet, dry, and convulsive, have been reported. The wet shock is the most desirable and the commonest type of reaction.

The sequence of events of wet shock is comparatively constant and typical and recapitulates briefly the response of the patient during the first few days of treatment. The patient passes through the stages of somnolence, sleep (patient can be aroused), incipient coma (patient cannot be aroused when called), sopor (deep sleep from which the

patient can be aroused by certain strong stimuli), and coma (patient can no longer be aroused by any stimulus). Likewise, progressive motor phenomena appear as successive levels of hypoglycemia are attained. These will be discussed in the order of their appearance. Motor restlessness and tremor, as previously mentioned, may occur in the early stages of treatment. This is followed by a mild degree of hypotonia and clonic twitchings. Incoordination, anomalies of tonic reflexes, choreic and myoclonic twitchings then appear and are followed by the disappearance of normal reflexes and the appearance of pathological reflexes. (Babinski, Oppenheim, etc.) There is then a disappearance of all spontaneous movement and of all defense reactions. Following this there is a diminution of muscle tone and a disappearance of tendon reactions. Finally the pathological reflexes disappear with areflexia and final general hypotonia. The pupils usually remain normal or slightly dilated. Marked contraction occurs only occasionally. Sakel notes very marked tonic attitudes and movements reminiscent of the decerebrate animal. (26,31,32,35,38) Various vegetative and vasomotor symptoms occur as a result of the hypoglycemia. The blood pressure usually varies within normal limits. Bradycardia first occurs, and this is then followed by

tachycardia during the stage of excitement. With the onset of coma the pulse rate is first decreased and it then returns to normal or above normal. The respiratory rate fluctuates within narrow limits. Deviations below the normal is not significant. Irregular, stertorous respiration during the comatose state is quite frequent. The temperature usually decreases. A drop from 98.6 to 93 or 94 is not infrequent. Perspiration and increased salivation is present in eighty eight per cent of the cases. Vasomotor disturbances including pallor, flushing and cyanosis may be manifested. (31,32,35) On the whole there is a tendency for the mental phenomena to follow a certain pattern. The subjective reaction occurring in phase I has already been discussed. Kepler and Moersch (38) report that some of their more lucid patients, in referring to their subjective impressions during insulin shock, state that they seem to be overtaken by a sense of intoxication which causes them to pass gradually into oblivion and which leaves them without any memory of the period of coma. Patients who have hallucinations almost never report them as occurring in shock, probably because of the partial amnesia which exists for the hypoglycemic period. Reference has already been made to the lucid interval. This first appears in immediate reaction to hypoglycemia,

either in the precomatose phase or immediately following the termination of the coma. Likewise it is in this phase that manifestations in the nature of acting out of the tendencies which seem to have a distinct bearing on the content of the patients psychosis are observed. These occur relatively late in the course of treatment. (26,30,31,32,38) In recovery from coma the subject exhibits the same symptoms as when entering the coma, but in the reverse order. The higher functions, especially speech, are the last to reassert themselves. The patient may exhibit motor aphasia for from fifteen to twenty minutes after he is otherwise fully conscious. (32) All of the previously mentioned symptoms may occur separately or in groups, and coincidentally or in succession. (31) In the ideal deep wet shock the subject is quiet and relaxed, sweats profusely in large drops and often drools saliva by the ounce. The pulse is full and generally slow. The early weeks of insulin shock therapy are usually stormy with diversified symptomatology. As the treatment continues and the symptoms vanish, a period of comparative quiet ensues, when the patients daily behavior shows only minor abnormalities and the shock is relatively calm throughout.

Occasionally the patient falls into coma with little or no sweating. When this reaction occurs it is termed

dry shock. This is usually associated with varying degrees of motor activity from single myoclonic twitchings to generalized myoclonic seizures with little or no cyanosis. The convulsive reactions will be considered later. In an attempt to convert this dry shock into a wet shock, Reese and Vander Veer (32) administered pilocarpine hydrochloride. They administered from one tenth to one fifth grain of pilocarpine hydrochloride from one to two hours after the administration of insulin to a patient who constantly manifested dry shock with epileptic seizures. This produced profuse diaphoresis and also prolonged the pre-convulsive period of coma for about an hour, but a convulsion always occurred if the shock was allowed to continue. (31,32)

The last type of shock to be mentioned is the convulsive or epileptiform seizure. There is little uniformity of opinion with regard to the incidence of this type of reaction. Rossman and Cline (41) report that seventy five per cent of their cases have had one or more convulsive seizures. Wortis et al (36) report that less than one third of their patients have had epileptic seizures. This reaction may be of variable appearance in some patients and of constant occurrence in others. In some patients it is impossible to find a dose of insulin that will produce coma without convulsions. Two types of epileptic seizure

may be described. The early epileptic seizure appears in dry shock, that is, before the end of the third hour after the injection of insulin. This reaction is characterized by pallor, tachycardia, cry, conjugate deviation of the head and eyes, tonic spasms followed by tonic-clonic spasms of epileptic type, cyanosis, and Babinski. These symptoms appear progressively, in the order named. The patients manifesting these reactions do not usually pass into deep coma, and these symptoms usually occur in light coma before the onset of deep coma. However, there is usually unconsciousness during and for a short time following an epileptic convulsion. This is followed by a clouding of the consciousness for a short time before the full recovery of consciousness. The late epileptic seizure appears in wet shock, that is, three hours or more after the injection of insulin. These seizures have manifestations similar to those of the early type, but there is a preponderance of tonic features in late epileptic seizure. The late epileptic seizure has a tendency to repeat itself and may result in status epilepticus. (31,36,41)

These convulsive seizures are regarded as a dangerous complication of therapy by some authors. Rossman and Cline (41) state that it has been their experience that this type of reaction is followed by definite improvement in

the condition of the patient. Gillies (43) reports a case of schizophrenia of one and one half years duration who, in the second week of insulin therapy, developed status epilepticus which was relieved by energetic therapy. This series of seizures produced almost complete cure. He states that six months later she was still mentally normal. Reese and Vander Veer (32) state that these reactions, if mild, should be allowed to continue for a while, as they may terminate spontaneously. They state that severe epileptiform seizures are rare, and demand immediate intervention and termination of the shock. They state that the appearance of convulsive reactions is by no means a bad prognostic sign. This type of reaction will be discussed with reference to complications of insulin treatment. Drabkin and Ravidin (44) suggest that the degree of hydration has a profound influence on the incidence of convulsions in insulin hypoglycemia. They state that the sequence of events leading to convulsions in insulin shock is as follows: (a) severe hypoglycemia; (b) anhydremia; (c) rise of spinal fluid pressure to a critical level and, (d) convulsion.

For convenience of description, I have classified the complications of insulin therapy in three groups. In the first group are included those complications

which are not necessarily confined to the period of hypoglycemia and which do not necessitate the termination of the shock. Complications that require early termination of the shock by feeding with the stomach tube comprise the second group. The last group consists of those complications in which immediate intervention is of vital importance. In this last group termination is accomplished by the intravenous administration of dextrose, by the intramuscular injection of epinephrine, by venesection, and by spinal tap (15 cc.) according to the severity of the complication.

Vomiting may occur at any time during the hypoglycemia, and may occur following recovery from the shock. This complication may become serious if persistent, as it prevents the oral administration of carbohydrates, and results in a loss of carbohydrates. The application of a hot water bottle on the abdomen, the administration of the usual carbohydrates in fractions, and the reduction of the insulin dose are usually efficacious in the control of this complication. Repeated elevation in the afternoon temperature is usually indicative of an overdose of insulin. As previously mentioned, salivation is one of the most frequent phenomena of insulin shock. Partial asphyxia may occur as the result of the accumulation of saliva in the

pharynx. Turning the patient on the side or stomach, to allow free drainage, is often enough to combat this condition; however, occasionally shock must be terminated. After-shock, that is the occurrence of a second shock occurring at a variable interval following the first shock, may result from the insufficient administration of carbohydrates or from the loss of carbohydrates through vomiting. This may be mistaken for normal sleep with the result that a dangerous hypoglycemia is produced. (31,32,34)

The hunger-thirst excitement which occurs early in the treatment is an indication for the early termination of hypoglycemia in the opinion of many authors. In some cases the administration of saccharin, diluted to a concentration of four grains to the quart, may quiet the patient enough for coma to appear. Tachycardia, fluctuations of the pulse rate between 90 and 180, irregular soft pulse, and prolonged inspiratory dyspnoea accompanied by moderate cyanosis are also indications for the early termination of shock. The shock should be terminated by feeding through the tube if sustained extensor spasms appear after the final hypotonic phase of the shock. (31,32)

Respiratory manifestations giving indication for the immediate termination of the shock include severe dyspnoea or apnoea, laryngospasm with associated signs of apnoea,

and Cheyne-Stokes or bronchospastic breathing. Cyanosis of the mucous membranes with a rapid, soft and thready pulse and vascular collapse as manifested by an irregular pulse and by bradycardia of under thirty five per minute likewise are indications for immediate termination of the shock. There is great diversity of opinion as to the implications and significance of epileptiform seizures. Early articles reported their occurrence to be of poor prognostic import, and they were classified as complications. The more recent trend is to include these seizures in the therapeutic regime, with only their late appearance (fourth to fifth hour) and the occurrence of status epilepticus being regarded as complications deserving of immediate termination of the shock. Likewise, protracted shock was previously considered as an indication for the immediate termination of the shock. As will be seen in the following section, this condition is being utilized in the treatment of the more chronic cases. (31,32,35,36, 41,42,43)

In recording the results of insulin shock therapy it is suggested by Muller that the patients should be classified as to the duration of their psychosis as follows: group I including illness of a duration of one half year; group II including illness of a duration of one year; group III

including illness of up to one and one-half years, and group IV including illness of over one and one-half years. Frostig suggests that the following classification of the degree of recovery be adopted: (a) complete recovery; (b) incomplete recovery; (c) partial recovery, and (d) no improvement. He recommends that the following four criteria for complete recovery be adopted: (a) complete disappearance of schizophrenic symptoms; (b) restoration of adequate emotional response; (c) critical insight into the past illness, and (d) full capacity for return to former work. The patient is said to have recovered incompletely when any one of the preceding requirements is lacking. The term partial recovery is applied in cases in which certain of the symptoms have disappeared or in which the patient shows partial improvement as manifested by pacification, social behavior and capacity for work. (31) No uniform method of recording the duration of the psychosis and no method of recording the degree of recovery has been adopted as yet. This makes an accurate evaluation of the results of this therapy impossible. Therefore, only the original statistics published by Dussick and Sakel, which have in the main been reliably substantiated, will be included. One hundred four cases comprise this group of which fifty eight were recent (duration under one-half year) and forty six were older cases.

In the group of fifty eight recent cases, a good recovery was made in eighty eight per cent enabling those patients to resume former occupations in the community, while in seventy per cent a complete recovery was made. In the group of forty six older cases (duration of illness of more than one-half year), a good social recovery was made in 47.8 per cent, whereas a complete remission was obtained in only 19.6 per cent of the cases. Of the good remissions, fifteen patients have been well for about a year, and thirty four patients have been well for more than one-half year. Of the group of recent cases there were nine relapses. Five of these patients were again placed on treatment, of whom three had a good recovery. (28,29) The mortality in Europe has been placed at 1.5 per cent. (32) The efficacy of this method of therapy is perceived when the above statistics are compared to the rate of spontaneous remission which is ten per cent. (45)

The clinical findings of the hypoglycemic state have been previously discussed. Attempts have been made to correlate the laboratory findings and the clinical manifestations. I shall not attempt to discuss the complete laboratory correlations. Only those of import from a therapeutic standpoint will be mentioned. We have seen that there is no constant relation between the dose of insulin and the

intensity of the reaction. Likewise there is no relation between the intensity of the reaction and the degree of hypoglycemia. To be sure, a drop of the blood sugar to below 60 mgm. % is an essential precondition for a clinical reaction. However, one repeatedly sees cases in whom a drop of the blood sugar to 30 mgm. % gives rise to no clinical manifestations. In such cases a reaction may occur following the administration of a larger dose of insulin. This increase in dosage does not lower the blood sugar level however. The deepest stage of insulin shock does not necessarily correspond with the lowest point of blood sugar content; on the contrary the blood sugar begins to rise at this particular point in most cases. Thus the blood sugar picture furnishes no indications as to the kind of clinical manifestations one might expect. Most likely it seems to be the case that a large part of the hypoglycemic symptoms are not due to hypoglycemia as such but are due to the reaction to the hypoglycemia, that is, to the compensatory secretion of adrenalin. According to Kugelman, the pounding of the heart, tremor, etc. are adrenalin symptoms, whereas the weakness, sweating, etc. are the direct result of the hypoglycemia. (35,39,46)

As study of the blood sugar during coma induced by insulin in schizophrenia has shown that the hypoglycemia

is never as low as the depth of the coma might let it be expected, Fisher (46) investigated the role of the sugar level of the cerebrospinal fluid. His findings indicate that the individual fasting values vary on a wide range. They are always higher than the blood levels and there is no evidence of a steady decline of them during subsequent comas. After the first hour the levels of the cerebrospinal fluid are much lower, and drop further, as fast as those in the blood. In the course of the second and third hour they drop faster than the blood levels, and in the first half of the third hour the declining curve approaches and often falls on or crosses that of the blood levels. In the second half of the third hour, while the blood sugar levels are on the increase and the coma is deepest, the levels in the cerebrospinal fluid continue to drop and the curves diverge definitely. At the end of the coma they begin to rise, but with a great individual range of variation, and always remaining lower than the blood levels. After the administration of sugar, the sugar levels in the cerebrospinal fluid recuperate very slowly although some of the patients are coming out of coma. A relation between the awakening and the sugar level of the cerebrospinal fluid is therefore completely out of the question. In certain cases the level remains low although the patient is wide awake and the blood shows hyperglycemia.

hyperglycemia. A hyperglycoorrhachia has not been reported. Dameshek and Myerson (47) demonstrated that following the administration of insulin the oxygen uptake by the brain was inversely proportional to the degree of the reaction. They report an increase of the spinal fluid pressure. Likewise they report that the administration of epinephrine regularly diminished the symptoms of the insulin reaction.

Hoagland et al (48) report the findings of the electrogram during insulin hypoglycemia. They have used the delta index as the criteria of reactivity. They find that the record is more "broken up" the deeper the coma, and that this breaking up may occur as long as one hour previous to evidences clinically observable. It was observed by them that the delta index in schizophrenic patients was much higher than it was in normal individuals. They report that the "post-sugar delta index" is less than the "pre-insulin delta index".

Numerous theories have been advanced to explain the mechanism of the neurologic symptoms. Fisher(46) states that the coma is due to the lack of sugar in the tissues, especially in the ganglial cells, and that this lack is not the cause but the effect of a more profound disturbance or dysfunction in the nutrition of the cells. He espouses the opinion of Georgi to the effect that sugar

streams from the cerebrospinal fluid and therefore also from the ganglial cells of the cortical region, into the impoverished blood. This transfer creates a "potential" which may, under certain circumstances, cause an epileptiform attack. Olmsted and Taylor (49) find that the blood becomes more concentrated when the blood sugar reaches its lowest level. They conclude that insulin convulsions are caused by increased cerebrospinal fluid pressure, resulting from anhydremia. The epinephrine theory, based upon the similarity of the reaction to epinephrine and to insulin is rendered less logical by the recent demonstration that the injection of epinephrine reduces rather than augments the symptoms of reaction. The anoxemia theory is based upon the diminution of the arteriovenous difference of oxygen content during hypoglycemia. (47)(38)

Sakel (30) assumes a progressive development in the cell of pathways which are specific to certain stimuli. He assumes a hierarchy of pathways. He believes that the older pathways are more resistive to insult. The more recently established pathways are more active and more sensitive to injury. Thus these recent pathways are the first to be affected by any insult to the organism. He believes that the changes occurring during hypoglycemia can be explained by the assumption that the hypoglycemia

blocades the pathways which happen to be most active at a given time, so that the reactions to the same stimuli, must come through pathways which had previously been inactive. He assumes that by keeping the pathologically conditioned cell pathways in abeyance the originally normally conditioned pathways have a chance to reestablish themselves. Qualitative injury to the nerve cell causes injury to the youngest pathways first. The older pathways become involved as the injury becomes more severe. Thus during insulin shock the recently established pathological pathways are eliminated and only the older well established pre-psychotic pathways survive and become re-animated.

Up to the present, there has been no unanimity of opinion regarding the existence of pathologic changes in the central nervous system resulting from hypoglycemia. Terplan reported extensive zones of degeneration in the cortex of the brain. Subarachnoid hemorrhage and hemorrhage into the brain have been discussed by Freed and Wofford. (50,51) Kepler and Moersch have noted areas of sclerotic nerve cells, zones of hyperchromatic changes in the cells and changes in the oligodendroglia and microglia following animal experimentation. These changes in the cells were noted to be most frequent in the third fifth layers of the cortex. (38)

Protracted Shock

Mention of the protracted insulin shock has been intentionally omitted in the previous section. This had been previously considered a complication of insulin shock therapy. At the present time it is being employed by some psychiatrists as a therapeutic procedure.

Kraulis (50) published an account of this method in May 1937. He was led to this method by the observation that certain cases who shortly after the beginning of the treatment, having undergone an unanticipated and an unwished for protracted shock (comatose state in spite of glucose administration and hyperglycemia), afterwards quickly improved and became continuously able to work. He has observed a total of 170 protracted insulin shocks in thirty two patients, and he admits that such states of protracted shock are dangerous as it is impossible to influence the course of the shock. More recent reports indicate that it is possible to control the course of the shock by the intravenous administration of crystalline vitamine B₁. (51,52)

Kraulis suggests that this method be used only on the otherwise hopeless cases of chronic schizophrenia. He selected only those chronic cases who were completely sound physically, with particular reference to the heart

and lungs. Further contra-indications will be considered in a discussion of technic.

The method consists essentially of prolonging the coma beyond the third hypoglycemic hour by the administration of small amounts of sugar by tube or by the administration of crystalline vitamin B₁. Thus a patient may be held in a comatose state for twelve or more hours in contrast to the one and one-half to two hours by the original method. According to Kraulis, less than twelve hour shocks have little or no therapeutic value. This treatment is given once weekly by him.

Kraulis suggests that, following a clinical examination of the patient, a functional test be made. This first protracted insulin shock is so conducted that the patient has only a superficial or slight coma. In such a condition the corneal reflex in both eyes must remain active, the patient may show only transitory respiratory respiratory disturbances and the blood sugar must not sink lower after the sixth hypoglycemic hour, following the usual dose of insulin. These conditions are attained through administration of sugar through the nasal tube which must remain continuously in place. Five grams of sugar is given immediately as soon as the patient no longer reacts to the introduction of the nasal tube.

Upon evidence that the patient is falling into a deeper degree of coma, five to ten grams of sugar dissolved in a little water is to be given repeatedly. The depth of the coma in such a procedure is so superficial that the patient often shows a tendency to awakening, and makes defensive movements when the mucous membranes are touched with cotton. Such superficial shocks have no therapeutic value, but they serve as a test of the function of the heart and respiration. These test protracted shocks are without danger for the patient and are easily terminated by the administration of sugar through the tube or by the intravenous administration of a small amount of glucose. If in the course of this shock a pulse rate of over 140 occurs, the pulse becomes irregular or there is a dropping of individual beats, and there is unequal filling, the protracted shock should not be undertaken. A variable pulse rate within 60 to 140 beats to the minute, whereby the pulse is full and is regular, is no contra-indication for the protracted shock. Even so, the respiration must remain deep, regular, and equal. With respiratory disturbances which are not relieved by small sugar doses, and also apnoea or Cheyne-Stokes' breathing, treatment with protracted shock must be avoided. A test protracted shock of from seven to nine

hours suffices in order to adequately evaluate the vegetative function, stability, and endurance of the patient. If the patient awakens before this time, the test shock must be repeated. (50)

If the patient is to be placed on this type of treatment, insulin in increasing doses is given as described in the section on insulin shock. After the shock dose is attained it is maintained and is never reduced. It has been found that increase in dose after a certain dose is reached results in no further reaction. On the day before treatment is commenced the patient receives his usual shock dose, and receives his last meal at four o'clock in the afternoon. The following day he receives the same dose of insulin or two or three units more at three o'clock in the morning. This dosage must be chosen so that the patient develops his first somatic reaction, tremor or clonic movements, after the second hypoglycemic hour. If these symptoms appear earlier, the dose chosen is too high, and then one may not carry out the protracted shock. Severe complications have resulted in such cases of too high dosage. (50,51)

Kraulis recommends that five grams of sugar be given when the patient no longer reacts to the tube. Blood sugar determinations are made every hour through-

out the treatment, but one should not be guided in a mechanical way by the sugar level. With the same depth of coma, the sugar level may be twenty or sixty milligrams per cent. Kraulis states that he has often seen threatening situations with 50 mgm. % and conversely, easier awakening with 18 mgm. %. A continued sinking of the blood sugar level, in spite of repeated sugar administration, is a dangerous sign. In such a case the shock should be ended. The influence of the oral sugar administration is usually seen in the blood sugar level after a lapse of from five to fifteen minutes. If, one hour after the last dose of sugar, the blood sugar level shows a rise of from fifteen to twenty milligrams per cent higher than the estimation one hour previously, then one should be careful about giving further sugar, because the patient may awaken with an additional dose of five grams of sugar. The ideal level of coma is reached when the patient does not react to the touching of the mucous membrane of the mouth and nose. The corneal reflex in both eyes need not be completely lost. Kraulis states that it is more advisable to give small doses of sugar frequently rather than large doses at longer intervals. Two hundred grams of sugar is used to terminate the shock. (50)

Rossman and Cline (51) recommend that the duration and intensity of the shock be controlled by the intra-

venous administration of crystalline vitamin B₁. They suggest that one milligram of vitamin B₁ (250 international units) together with intravenous glucose be given as soon as the reaction is established. This may be repeated, if necessary, after a few hours.

Spontaneous awakening may be considered as a complication. This frequently occurs when the patient has become accustomed to the dose of insulin. In such a case the dose should be increased by as much as twenty units. Respiratory disturbances are the most frequent complication, and if severe, give indication for termination of the shock. Cardiac complications, epileptic attacks, conjugate deviation, clonic convulsions of the whole body, and other severe organic brain symptoms are of more serious import and give indications for immediate termination .

The results obtained with this type of therapy are encouraging. Rossmann and Cline report a series of fifty-two male patients, in whom the average duration of the psychosis was 4.1 years, that received this method of therapy. They report that 11.5% recovered, 28.8% were much improved, 42.3% were improved and 17.4% were unimproved. (51,52)

COMBINED THERAPY

A combination of insulin and metrazol therapy has been found advantageous in the treatment of some cases. Reese (22) notes that in stuporous, depressed, or catatonic patients a drastic metabolic shake up with metrazol appears necessary to effect a response more favorable to insulin shock therapy. He recommends that when one method fails, the other should be tried. Young and Young (14) cite five groups of patients in whom this combined therapy has been applied. The first group consisted of patients who, after approximately three weeks on insulin, failed to show progress and were then given a series of metrazol treatments. In the second group of schizophrenic patients metrazol was given after their failure to attain coma on a dose of 200 units of insulin or over. They used metrazol in such cases as a less dangerous medicament. A third group of patients were given small doses of insulin in addition to the metrazol. In these patients insulin was added to the treatment because in the early experience of giving metrazol alone the authors found that some who showed no progress made prompt improvement when insulin was added. The fourth group received insulin in order to alleviate the fear of metrazol treatment. In the last group metrazol was given after the patients had failed to improve on a full course of insulin.

Himwich (53) compares insulin and metrazol therapy. He states that a similarity in the two forms of treatment lies in the fact that both depress the metabolism of the brain. The brain differs from other organs in that it uses only carbohydrates to furnish the energy required. When hypoglycemia supervenes the brain is therefore deprived of its only source of energy. Cerebral metabolism is therefore depressed, and under these conditions, first excitement and then coma supervenes. Metrazol convulsions are also characterized by depression of the metabolism of the brain. This is not caused by a diminished dextrose uptake but by a decrease in the oxygen supply. During the convulsion there is a cessation of respiratory movements so that the arterial blood becomes venous and the brain is deprived of oxygen. Thus the two treatments have in common a depression of cerebral metabolism. Hypoglycemia produces a slow, gradual and prolonged depression. Metrazol convulsions, on the other hand, cause a severe deprivation of oxygen and therefore necessarily must be briefer. The two actions may be combined and they are synergistic. To the slow, gradual hypoglycemic effect is added the brief, acute deprivation of oxygen. It may be concluded that the deprivation of cerebral energy is associated with the initiation of the changes which cause the amelioration.

ESTROGEN

The mental changes accompanying the menopause may be mild or exaggerated. When exaggerated the diagnosis of involutional melancholia is made. Estrogen has recently been reported of therapeutic value in the treatment of these mental aberration occurring coincident to or following the menopause. Ault et al (54) state, "For all practical purposes theelin seems to be specific in involutional melancholia. Theelin is indicated for any woman during the climacteric having disturbed mental aberration, whether mild or severe". Mayer and Israel (55) have applied this therapy in a group of patients presenting climacteric symptoms bordering on involutional melancholia with resulting good therapeutic effect. Also Ault and associates (54) report that patients institutionalized because of previously developed mental illness become "disturbed" with the advent of the menopause and have quieted down when given theelin. Werner et al (56) emphasize that the stresses of the menopausal and post-menopausal periods may cause dormant psychotic tendencies to develop into definite psychoses. Thus a schizoid personality, under these conditions, may develop into a typical case of schizophrenia.

There are apparently no contra-indications to this therapy. Werner found that usually only those patients in

whom estrogen is being excreted in the urine fail to respond to theelin therapy; this group comprised not more than ten per cent of his cases. Likewise where mental deterioration has resulted from the long duration of the disease process, the prognosis is poor.

Methods of administration include oral administration, hypodermic injections and intramuscular injections. The estrogens are available in pure crystalline forms as keto-hydroxyestrin (theelin) and trihydroxyestrin (theelol). The international unit of estrogenic potency is the effect produced by 0.1 gamma (0.0001 gram) of theelin. The relation of animal units to the international unit is quite variable depending upon the manner of bio-assay. Mouse units and international units are accepted as being about equal, and a rat unit is approximately equivalent to five international units. (57,58) In this paper, dosage will be expressed in international units using the above estimations in translating from mouse and rat units.

The rate of absorption, continuity of action, and physiologic effect of the estrogens are influenced by the vehicle used and by the site of injection. Water soluble preparations, which are more rapidly absorbed and excreted, require more frequent injections and larger dosage. Oily solutions are taken up more slowly than aqueous solutions. The rate of absorption is more rapid from muscle than from the subcutaneous tissues.

Administration of theelol by mouth is practical and is usually preferred by the patient. It does not, however, permit as accurate dosage as does the parenteral route.

(57) Theelin in oil is prepared so that 1 cc. contains 1.0 mg. (10,000 international units) and theelol is prepared so that one capsule contains 0.24 mg. (2,500 international units).

No precise rules can be laid down for dosage or methods of treatment, since endocrine imbalance can occur at very different quantitative levels. Often rather small doses of estrogenic substance may be adequate in treating borderline conditions. (59) Werner et al (60) in reporting a series of forty cases of involutional melancholia set the dosage at 1 cc. of the aqueous solution (Theelin, Parke Davis, 250 international units) daily for six months. They find that the administration of 1 cc. of Theelin in Oil (Parke Davis) given intramuscularly twice weekly is just as effective as the daily dose of 1 cc. of the aqueous solution also given intramuscularly. Suckle (61) reports a case in which progynon (Schering, 225 international units) was administered twice a day per os. This was increased within a month to 1000 international units twice a day. This therapy was supplemented by as many as 25,000 international units of estradiol benzoate as frequently as every week. Ault et

al (54) recommend an initial dosage of from 30,000 to 40,000 international units of theelin in oil in all types of cases during the first month. This can be conveniently divided into doses of 5000 units of theelin in oil intramuscularly, twice weekly. Subsequent dosage was adjusted to meet the patients needs. Fluhman has injected as many as 20,000 units every three or four days for several weeks. (62) Werner in a recent article (63) recommends a larger dose of from 1000 to 2,000 units of estrogenic hormone as often as three times a week, and, in some cases, as much as 2,000 units daily during the first month with subsequent reduction. As soon as an unmistakable response is obtained, the dosage may be gradually reduced, but theelin administration should probably be continued for several weeks after adjustment has apparently been made and recovery from the psychosis taken place. Werner et al (60) and Suckle (61) advise a course of intensive therapy. Werner et al (60) consider six months necessary for a therapeutic test of the efficacy of theelin in individual cases. Only by observing the patient when treatment has been discontinued is it possible to determine when theelin may be permanently discontinued. In a series of fourteen institutionalized cases, Ault et al report definite improvement in two cases as early as one month following institut-

ion of theelin therapy, and slight improvement in a third. In only four patients was treatment continued beyond three months. Of these three were treated for six months, and one was treated for ten months. All four were reported as showing marked improvement. It has been suggested that theelol per os be administered during the process of theelin withdrawal after menopausal and mental symptoms have been brought under control. It is also advocated as supplementary to intramuscular therapy. As much as 2 mg. per day may be administered.

Ault et al (54) report a recovery rate of ninety two per cent in their series of cases. Mazer and Israel report a series of thirty three borderline cases, all of which responded to estrogenic therapy irregardless of the severity of the symptoms. Werner et al (56) report a series of forty patients. Twenty of these were given 1cc. of theelin in aqueous solution intramuscularly daily for six months. The other twenty cases were used as controls and were given 1 cc. of physiologic sodium chloride intramuscularly daily for the same period of time. After the control patients had failed to benefit by the injections of physiologic sodium chloride, they were given 1 cc. of theelin intramuscularly daily for six months.

In the first twenty patients treated with theelin, marked improvement was shown in 61.9%, moderate improvement in 14.2% and no improvement in 9.5%. In the control patients marked improvement was shown in no case, moderate improvement was shown in 10.5% and no improvement in 84.2%. In these control patients, after receiving theelin, marked improvement was shown in 44.4%; moderate improvement in 27.7%. In this control group involutional melancholia complicated by other forms of mental disease was present in 27.7%.

By marked improvement these workers assume that the patient has recovered sufficiently to lead normal social lives. Of the total group, these workers report a marked improvement in 65.55%. (56)

These authors believe that with continued therapy the group showing moderate improvement will continue to improve. They also advocate the administration of theelin in oil intramuscularly (1 cc. i. e. 1500 units) weekly for an extended time after the preliminary treatment to prevent relapse in patients whose syndrome will be of long duration. After discontinuance of medication it should be promptly reestablished in the face of a relapse. (56)

Werner et al (56) conclude that theelin in curative in cases of uncomplicated involutional melancholia, that theelin accelerates recovery and shortens the period of

mental illness, that the prognosis is favorably influenced by early diagnosis and treatment, that a history of previous mental disorder in the patient suggests a guarded prognosis, and that the administration of theelin may be used as a therapeutic diagnostic test to differentiate between involutional melancholia and other types of mental disease occurring at the menopause.

The rationale of this therapy is somewhat problematic. Fluhman (64) noted that following the anterior hypophysis hypertrophies and that there is an increase in the amount of gonadotropic hormone in the blood serum of many of these women. Mazer and Goldstein (65) note that the ovarian follicular hormone, estrogen, on the other hand decreases. Werner et al (60) state that during the menopause there is a complex endocrine crisis in which the predominating feature is gonadal insufficiency, and that other glandular disturbances occur subsequently and form an essential part of the complex. This includes imbalance in other interrelated glands such as the anterior lobe of the pituitary, the thyroid, and the adrenal. He states that most of the symptoms are a result of the instability of the autonomic nervous system resulting secondarily from the disturbance of the endocrine glands.

BENZEDRINE

Benzedrine, beta-amino-propylbenzene or benzyl-methyl carbinamine, has been found to possess a sympathomimetic action and a profound stimulating effect on the central nervous system. It has been found to have an ameliorative influence in certain conditions including chronic exhaustion (66,67,68), disorders of mood and affect (66,67,68,69,70,71), certain cases of psychoneurosis (68), and narcolepsy (67). The drug apparently is of little value in schizophrenia including catatonic states and hebephrenia. It is probable that eventually benzedrine will be found to have its greatest value in the treatment of chronic exhaustion or depression when it is used temporarily or perhaps intermittently. (66) Wilbur et al (66) report that the immediate effects of the oral administration of benzedrine in cases of chronic exhaustion, depression and psychoneurosis were beneficial to approximately eighty, seventy and forty six per cent of the cases respectively. Prinzmetal and Bloomberg (72) state that benzedrine is approximately three times as effective as ephedrine in preventing attacks of sleep in narcolepsy, and that in some cases it gives complete relief of symptoms that are not relieved by huge doses of ephedrine.

There appear to be but few definite contra-indications to benzedrine therapy. When symptoms such as nervousness, anxiety, restlessness and irritability are present they are frequently uninfluenced or even accentuated. Wilbur et al state that the drug does not appear to be toxic in usual doses and that it does not seem to be habit forming. As to the continued use of this drug they are less optimistic. It is their opinion that it is unwise to recommend the continuous use of benzedrine except to patients who are less than sixty years of age, who present no evidence of hypertension or cardiac disease and who can be closely watched by the physician. They report that in patients suffering from psychoneurosis with dominant symptoms of nervousness and anxiety, inability to relax and lack of energy, the symptoms are accentuated by the administration of benzedrine. Because of this they do not recommend the prolonged administration of benzedrine to this group. Likewise Apfelberg (73) reports a case of benzedrine poisoning in a psychoneurotic and Anderson and Scott (74) describe a case presenting very severe cardiovascular symptoms in a patient with involutional depression following benzedrine therapy.(66)

Wilbur et al (66) reporting a series of one hundred patients diagnosed as chronic exhaustion, psychoneurosis, and depression used an initial oral dose of benzedrine

sulfate ranging from two and one-half to twenty milligrams before breakfast, repeating the dose at noon if necessary. The usual dose ranged from ten to twenty milligrams. They report that if the drug is taken later than noon, insomnia usually results. It is their experience that if the condition of the patient fails to improve following the administration of one of the doses noted he will not be benefited by a larger amount of the drug. Likewise the effect of benzedrine therapy will be as pronounced on the first day as it will be on subsequent days. Thus the effects of its administration can be determined in one day. If there is no beneficial effect from its administration before breakfast and lunch on one day, it appears useless to administer it over longer periods. Many of the patients with exhaustion and depression whom they have observed and who have taken benzedrine over a period of weeks or months have found that they were able to reduce the dose to as little as from two and one-half to five milligrams before breakfast, with continuation of good results. In other cases ten milligrams in the morning and from two and one-half to five milligrams at noon will maintain a favorable effect. Occasionally patients find that intermittent use of the drug proves more satisfactory than continuous administration.

Solomon et al (75) have given as much as 160 mg. a day, apparently in divided doses, for three weeks, without apparent harmful effect. Davidoff and Reifenstein (76) have administered 200 mg. in one day to a patient without a resulting severe reaction. Prinzmetal and Bloomberg (72) in the treatment of narcolepsy with benzedrine used doses varying from ten to forty milligrams three times daily depending upon the age of the patient and the severity of the disease. Peoples and Guttman (77) gave doses of from ten to eighty milligrams to twenty five persons noting usually a rise in blood pressure and pulse rate with no other cardiovascular phenomena. Hartung and Munch (78) find that the minimum lithal dose of benzedrine hydrochloride is twenty five milligrams per each kilogram of body weight of rats.

Although benzedrine has an apparently large pharmacological margin of safety, it must not be inferred that its administration is not attended without toxic manifestations. Such manifestations as cardiovascular disturbances, exhaustion and fainting or else collapse have been noted in the more severe reactions. (73) The case of benzedrine poisoning reported by Apfelberg (73) demonstrates that the drug may become lethal, at least in some individuals, in far smaller doses than those

computed by experimental ratios deducted from its effects on animals. In this case, the patient, diagnosed as a psychoneurotic, had evidently taken 140 mg. of benzedrine in a single dose. Upon arrival at the hospital he was in a comatose state from which he could not be aroused. Prior to admission the family had noted loss of sphincter control and the occurrence of several convulsive attacks. Upon admission to the hospital the patient was in a condition of shock; the skin was ashy pale, the extremities cold and clammy, the pulse was not perceptible, the cardiac rate was sixty, and the blood pressure was 100/70. The temperature was 94.4 F. and the respiratory rate varied between eighteen and twenty four. Tremor of the upper extremities and fibrillary twitchings of the muscles of the jaw were observed together with a Babinski sign on the right and a Hoffman sign on the left. The pupils were mid-wide and equal and reacted to light. There was no nystagmus. The patient recovered from coma about thirty six hours after admission but was mildly confused, retarded, and depressed for a day, after which mental clearness continued. Subsequently, following a course of stomatitis, hematuria, and pneumonia, the patient made a complete recovery within ten days following admission. (73) Anderson and Scott describe a case presenting very severe cardiovascular

symptoms following the use of thirty milligrams of benzedrine sulfate. This patient, who was suffering from involutional depression with paranoid ideas, became dyspneic and flushed two and one-half hours after benzedrine was taken. Several hours after that there was collapse cyanosis, clamminess and a slowing of the pulse rate to fifty six with a lapse of every fourth beat. In reviewing the literature they state that nowhere else did they find such severe cardiovascular effects.

Myerson (68) has made a study of the effects of benzedrine sulfate on mood and fatigue in normal and in neurotic persons. He states that the normal non-psychotic and non-neurotic persons who suffer from fatigue and slight malaise due to insufficient rest receive immediate benefits and relief of a pleasant type when from five to twenty milligrams of benzedrine sulfate is taken on arising. Bradley (80) states that the result is felt within thirty to forty five minutes and the maximum reaction occurs during the second or third hour following the administration. He states that within sixteen hours there is complete subsidence of the effect of this drug. Myerson states that a dose of from five to twenty milligrams taken by mouth causes a warm glow which is agreeable and

which is associated with a sense of relaxation and at the same time results in the disappearance of the tired feeling around the face and eyes. According to him, the effect lasts from two to several hours. With a larger dose the subject may feel "jittery", and may have a sense of over-tension and excitability.

The reaction, in patients diagnosed as chronic exhaustion, is variable. In some instances it resulted in a complete disappearance of exhaustion, marked exhilaration and increased capacity for physical and mental work. Along with this there were, in some cases, extraversion of thought and activity, speeding up of mental processes, cheerfulness, elation and loquaciousness. Vague neuromuscular aches and pains and consciousness of abdominal discomfort frequently were greatly benefited or entirely relieved. When symptoms such as nervousness, anxiety, restlessness and irritability were present they were frequently uninfluenced or even accentuated. Many of these patients stated that they felt "jittery" or stimulated and that they noted dryness of the mouth, palpitation, tremor and excessive sweating. In states of depression the patients become happy and confident and there was an increase in psychic and motor activity.

Wilbur et al (66) in their series of one hundred cases classified their patients as: first, chronic exhaustion, characterized by persistent sensations of fatigue, lack of energy and lassitude for which no organic cause can be demonstrated; second, psychoneurosis, characterized by nervousness, anxiety, restlessness, irritability, inability to relax, and numerous somatic symptoms in which fatigue is not a prominent symptom, and third, depression with mental and physical slowing being the predominant feature of the clinical picture. All of these patients were carefully examined and had no detectable evidence of organic disease. They report that in cases of chronic exhaustion forty eight per cent of the cases are continuing to use benzedrine after periods of from one to eight months and feel that the favorable effects have persisted. Twenty two per cent felt improved during the use of this drug for from one week to one month, but discontinued its use because unpleasant effects noted previously continued, and offset the beneficial results. Improvement of the condition of thirty per cent of these cases continued for from three weeks to four months while they used the drug, but they discontinued the use of it after variable periods because improvement was only slight, because of subsequent development of undesirable symptoms or because the effect

of the drug wore off entirely. A review of the records of the patients whose condition was improved and of those for whom improvement was only temporary or was associated with unpleasant symptoms failed to reveal any distinguishing features that could be used to explain the divergent results. It may be inferred that idiosyncrasies to smaller doses and also resistance to larger doses in this condition is apparently a factor influencing the psychosomatic reactions in different individuals. In the patients diagnosed as psychoneurosis, prolonged administration of benzedrine was discontinued as many of these patients noticed that unpleasant symptoms of this condition were accentuated by the administration of the drug. If exhaustion was present, frequently it was improved, but the dominant symptoms were frequently exaggerated. Likewise in the group classified as depressions the results of the prolonged administration of benzedrine were disappointing. Of these cases twenty four per cent had used the drug for six months and continued to obtain relief. Five per cent obtained relief for from three to six months. Fourteen per cent obtained relief for three months. Twenty eight per cent obtained relief for one month and another twenty eight per cent obtained relief for only one week. Thus it is obvious that relief of depression as a result

of the administration of benzedrine is temporary in many instances. The treatment is variable with each patient, some patients receiving marked benefit from prolonged administration in which instances its use should be continued.

The results of the prolonged administration of benzedrine are more encouraging. It should be mentioned that the classification of this syndrome of somnolence, and cataplexy as a neurosis is at the present time debatable. Recent observers believe that actual pathological changes are present. (79) The first patient with narcolepsy to whom Prinzmetal and Bloomberg (72) reported giving the drug has continued taking the same dose of the drug after three years. They conclude from their series of cases that in all instances complete relief from the attacks of sleep and practically complete relief of cataplexy results when suitable doses of benzedrine are given. They find that, on the average, this compound is three times as effective as ephedrine. They have observed no diminution in the effectiveness of benzedrine when given over comparatively long periods of time.

The results of the prolonged administration of benzedrine have been discussed with relation to duration of treatment. The immediate effects are more encouraging.

Wilbur et al (66) report that the immediate effects of the oral administration of benzedrine in their series of one hundred cases were beneficial in eighty per cent of the patients suffering from chronic exhaustion, in seventy per cent of those with depression and in forty six per cent of those suffering with psychoneurosis. Of the patients initially benefited about fifty per cent of those who had chronic exhaustion and about twenty five per cent of those who had depression continued to receive benefits for periods of from one to eight months. Myerson (68) states that in certain cases of the neurosis associated with depression, fatigue and anhedonia, and in certain cases of the minor stages of the psychosis of the same general type, benzedrine acts as an ameliorative influence. He states that as it helps to dissipate the morning apathy and depression its ameliorative effect is sufficiently important to recommend it during the treatment of the patient by other means and while the process of natural recovery is taking place. In his opinion benzedrine does not fundamentally and permanently alter a psychotic disorder or a state of chronic exhaustion. It is not in any sense curative and its effects are not permanent.

the toxic manifestations, that may result following the administration of benzedrine have already been

discussed. Unfavorable gastro-intestinal symptoms including abdominal cramps and an increased desire to go to the stool have also been noted.(76) Loss of weight, apparently resulting from reduced appetite and increased activity, may occur.(66,67,76)

The method by which benzedrine produces a stimulating action on the central nervous system and the part of the brain it stimulates is unknown. Marked stimulation of the nervous system is the most striking effect of the drug. The long duration of the effect is noteworthy. Wilbur et al state that while it appears to them that in states of exhaustion benzedrine may simply decrease awareness of fatigue, they are uncertain whether this is the result of stimulation of the central nervous system or of sympathomimetic activity. (66) It is evident that its action is that of stimulation. Whether it is logical and safe to continuously stimulate individuals who present such disturbances is a question that has not been answered as yet. It should be kept in mind that it is possible that the abolishment of the sensation of fatigue and exhaustion may result in the expenditure of energy beyond the capacity of the individual.

SUMMARY

With mental patients occupying fifty five per cent of all available hospital beds in the United States, with the incidence of potential mental disease in the United States being placed at one in every twenty six individuals, and with functional mental disorders constituting forty six per cent of all forms of mental illness, the treatment of these functional disorders is assuming great importance.

Of equal significance is the fact that with modern methods of therapy between sixty five and seventy five per cent of these patients may recover. The paramount importance of the early institution of therapy in these conditions is evidenced by the comparison of recovery rates of acute and chronic cases. It may be concluded that the rate of remission and the degree of recovery is inversely proportional to the duration of the illness.

Within the last decade drug therapy as adjuncts in the treatment of these patients was instituted. Insulin in shock producing amounts and metrazol were found to be of value in the schizophrenic group of psychoses; metrazol and camphor were found to be of value in the depressive states and in certain of the psychoneuroses;

estrogenic substances were found to be of value in the treatment of involutional melancholia and benzedrine was found to be of value in treating narcolepsy and certain of the psychoneurosis.

It was not the authors intention to imply medical therapy to be the panacea of functional mental disease. That these methods may serve as valuable adjuncts in the treatment of these patients is evidenced by the statistics furnished.

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